REMARKS

Claims 9-14 and 18-21 are pending and under Final Rejection in the application. Claim 21 is canceled herein. Since prosecution on the merits is closed, Applicants herein are filing a Request for Continued Examination under 37 CFR 1.114. A submission in the form of new arguments and the cancelation of claim 21 accompanies this filing. Reconsideration of the application is hereby respectfully requested.

I. Rejection of claim 21 under 37 CFR Section 112/2d Paragraph

The Examiner rejected claim 21 allegedly for failing to comply with the written description requirement. Specifically, the Examiner states that "the phrase 'optionally' has no support in the specification, it constitutes a new matter." Applicants have canceled claim 21 without prejudice to their ability to re-introduce it at a later time.

Applicants request reconsideration of the application on that basis.

II. Rejection of claims 9-14, 19-21 under 35 USC Section 103(a)

The Examiner has rejected claims 9-14 and 19-21 under 35 USC 103(a) as being rendered obvious by Schwartz US 4,886,741. Applicants traverse this basis of rejection, for the following reasons.

Schwartz et al. is disclosed and discussed by applicants on page 4 of the application. US Patent No. 4,886,741 (Schwartz et al.) describe the use of dextran sulfate, sodium salt, for use as a volume exclusion agent for ISH. The average molecular weight of dextran sulfate used by Schwartz is not described, but by reference to the source (Sigma Chemical, Products for Life Sciences, St. Louis, MO) it has an average molecular weight of 500,000. Schwartz et al. also disclose that dextran sulfate is typically used at a concentration of about 5-10% (w/v). Contrary to the Examiner's assertions, Schwartz et al. do **not** disclose *low molecular weight* dextran sulfate for use as an exclusion agent in polynucleotide hybridization. In fact, Schwartz et al. describe three different polymers useful as volume exclusion agents, including polyethylene glycol, anionic polymers of polyacrylate or polymethylacrylate, and generic dextran sulfate. It is not clear from the reference what molecular weight ranges cited apply to which categories of volume exclusion agents, but it is clear that low molecular weight dextran sulfate is not specifically called out either in col 3. lines 1-23, or any of the other places cited by the Examiner. The reference repeatedly mentions "10% dextran sulfate" (col. 9, line 26; col. 10, line 24-25) but does not specify the molecular weight. In the absence of any

indication to the contrary, one of ordinary skill would assume that the dextran sulfate being used was the 500,000-2,000,000 MW version, which is what is normally available in labs.

The Examiner's assertion that "The preferred polymer weight is at least 10,000 daltons" is misleading. What the reference actually says is the following:

> The preferred polymer weight is at least 10,000 daltons, and no more than 2,000,000 daltons, with preferred weights being between 100,000 to 1,000,000, especially for the polyacrylate and polymethylacrylate polymers. The most preferred weight for the polymers is between 400,000 to 600,000 daltons.

Schwartz, col. 3 lines 14-18. First, Schwartz is referring to any of three possible polymers, and not dextran sulfate specifically. Next, the citation to 10,000 daltons merely establishes the bottom molecular weight of the range for all of the polymers. And, the actual preferred molecular weight range disclosed by Schwartz is 400,000 to 600,000, which is taught in the last line of the above excerpt. Therefore, the Examiner is taking the statement that "the preferred polymer weight is at least 10,000 daltons" out of context. It is clear that Schwartz taught that the real preferred range was in the middle, i.e., 400,000 to 600,000. As such, Applicants discovery that low molecular weight dextran sulfate is particularly useful as a volume exclusion agent in the unique environment of Applicant's automated stainers is fully supported by the specification, and is not rendered obvious by this generic description of the state of the art in 1987.

Applicants previously limited the sole independent claim, claim 9, by adding the low molecular weight range specified, and therefore distinguished over Schwartz et al. Therefore, the claims as previously amended are not rendered obvious by the reference. Applicants also point out that the claims were previously limited to "**automated** in situ hybridization" which further distinguishes the claims over Schwartz et al., which teaches a manual procedure.

Applicants previously more clearly defined their invention by changing the form of the claim to Jepson format, thereby defining the background of the invention and placing the improvement in that perspective. The preamble defines the automated environment in which the claimed hybridization buffer finds it utility, and therefore distinguishes over Schwartz et al. which recites manual hybridization procedures. The Ventana-automated tissue staining environment includes the unique (and patented, see US 5,225,325) LIQUID COVERSLIP™ method to inhibit evaporation of liquid off the tissue or target during incubation at the high temperatures required for *in situ* hybridization. In particular, method claim 9 was previously amended to add "said method executed in an automated staining system having evaporation inhibitor liquid covering a polynucleotide hybridization buffer-

covered target on said slide." This language finds support on page 8, lines 24-31 wherein Applicants discuss the automated mixing environment by use of the LIQUID COVERSLIP™ (essentially a layer of mineral oil covering the aqueous layer over the tissue or target) with air jets to rotate/counter-rotate the solutions on the slide, thereby effectively mixing the aqueous phase. It was discovered by Applicants that standard hybridization buffers did not operate well in Ventana's environment due to the high viscosity of these buffers. The high viscosity inhibits the mixing and dispersion of the probe reagents when dispensed through the mineral oil layer into the buffer/tissue layer. Consequently, Applicants defined the problem (high viscosity), and then found the solution-a low-viscosity buffer that would still have the necessary volume-exclusion effect for optimal hybridization. Not only does the Schwartz reference not teach low-molecular weight buffers, they do not appreciate Applicants' fundamental discovery: that high viscosity inhibits hybridization in Ventana's automated environment.

The Examiner acknowledges that Schwartz et al. do not appreciate the unique limitations inherent in Applicant's automated staining environment. However, the Examiner then cites *In re Venner* for the proposition that "broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art." MPEP 2144.04 (III). Reliance on *Venner* is misplaced because Applicants claimed invention does not replace a manual activity with an automated one. Applicants are claiming an improved method of *in situ* hybridization in an automated tissue staining environment by automatically hybridizing a target with a polynucleotide probe composition in the presence of low molecular weight dextran sulfate having a molecular weight range from about 8,000 to about 16,000 daltons. The Examiner seems to be arguing under *Venner* that Applicants merely automated a manual method, while that is not the case. There was no manual method of ISH using low molecular weight dextran sulfate to be automated.

Similarly, the Examiner relies on *In re Aller* for the proposition that Applicants, in selecting low molecular weight dextran sulfate, routinely optimized the molecular weight ranges thereby attaining the desired goal. Again, reliance on *Aller* is misplaced because if Applicants had routinely optimized, they would have changed the concentration of the exclusion agent, as varying the molecular weight was not taught in the prior art of ISH. Routine optimization only applies where the "general conditions of a claim are disclosed in the prior art." One of ordinary skill in the art of molecular biology would not seek to vary the molecular weight ranges of dextran sulfate in order to determine the optimal weight for ISH.

Applicants have selected a low molecular weight range of dextran sulfate which is surprisingly advantageous given the prior art teaches away from the use of dextran sulfate due to its high viscosity at high concentrations. For instance, it was recognized by Brigatti in US 5,116,727 that increasing concentrations of dextran sulfate should be avoided in capillary gap environments due to the increased viscosity associated with it. See '727 patent, col. 1 line 67 – col. 2 line 6. Applicants' environment is very similar to a capillary gap environment due to the small (300 ul) available volume for reaction.

Applicants respectfully assert that the rejection of the claims for obviousness has been overcome by the arguments above, and reconsideration of the application is therefore requested.

III. Rejection of claims 9-14 and 19-21 under 35 USC 103(a)

The Examiner has rejected claim 18 as obvious in light of Schwartz et al. US 4,886,741 under 35 USC 103(a) and further in view of Towne et al. US 6,855,552, issued 2/15/05. Applicants traverse the rejection of claim 18 for the following reason.

The Towne et al. reference only qualifies as prior art under 35 USC 102(c), as its publication date (2/15/05) is subsequent to Applicants' filing date (8/28/03). Therefore it is not prior art under either 102(a) or 102(b). The '552 patent is assigned to Ventana Medical Systems, the owner by assignment of this pending application. The '552 patent and this pending application were under an obligation of assignment to Ventana Medical Systems, Inc. at the time the claimed invention was made, and so Applicants aver that the Towne et al. reference is disqualified as prior art against this application under 35 USC 103(c).

Applicants respectfully assert that the rejection of claim 18 is deficient, and therefore there is no prima facie case of obviousness. Applicants request reconsideration of the application on that basis.

Respectfully submitted,

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